

EXHIBIT C

CDC GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

Promoting Patient Care and Safety

THE US OPIOID OVERDOSE EPIDEMIC

The United States is in the midst of an epidemic of prescription opioid overdoses. The amount of opioids prescribed and sold in the US quadrupled since 1999, but the overall amount of pain reported by Americans hasn't changed. This epidemic is devastating American lives, families, and communities.



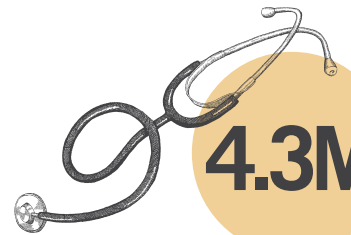
40

More than 40 people die every day from overdoses involving prescription opioids.¹



165K

Since 1999, there have been over 165,000 deaths from overdose related to prescription opioids.¹



4.3M

4.3 million Americans engaged in non-medical use of prescription opioids in the last month.²

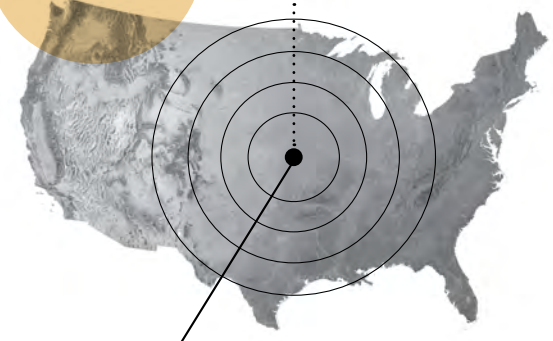
PRESCRIPTION OPIOIDS HAVE BENEFITS AND RISKS

Many Americans suffer from chronic pain. These patients deserve safe and effective pain management. Prescription opioids can help manage some types of pain in the short term. However, we don't have enough information about the benefits of opioids long term, and we know that there are serious risks of opioid use disorder and overdose—particularly with high dosages and long-term use.

R_x

249M

prescriptions for opioid pain medication were written by healthcare providers in 2013



enough prescriptions were written for every American adult to have a bottle of pills

¹ Includes overdose deaths related to methadone but does not include overdose deaths related to other synthetic prescription opioids such as fentanyl.

² National Survey on Drug Use and Health (NSDUH), 2014



**U.S. Department of
Health and Human Services**
Centers for Disease
Control and Prevention

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

NEW CDC GUIDELINE WILL HELP IMPROVE CARE, REDUCE RISKS

The Centers for Disease Control and Prevention (CDC) developed the *CDC Guideline for Prescribing Opioids for Chronic Pain* (Guideline) for primary care clinicians treating adult patients for chronic pain in outpatient settings. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care. The Guideline was developed to:

- Improve communication between clinicians and patients about the benefits and risks of using prescription opioids for chronic pain
- Provide safer, more effective care for patients with chronic pain
- Help reduce opioid use disorder and overdose

The Guideline provides recommendations to primary care clinicians about the appropriate prescribing of opioids to improve pain management and patient safety. It will:

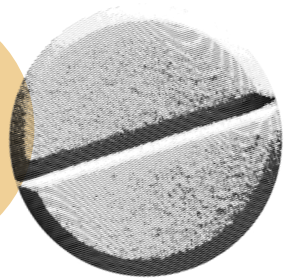
- Help clinicians determine if and when to start prescription opioids for chronic pain
- Give guidance about medication selection, dose, and duration, and when and how to reassess progress, and discontinue medication if needed
- Help clinicians and patients—together—assess the benefits and risks of prescription opioid use

Among the 12 recommendations in the Guideline, there are three principles that are especially important to improving patient care and safety:

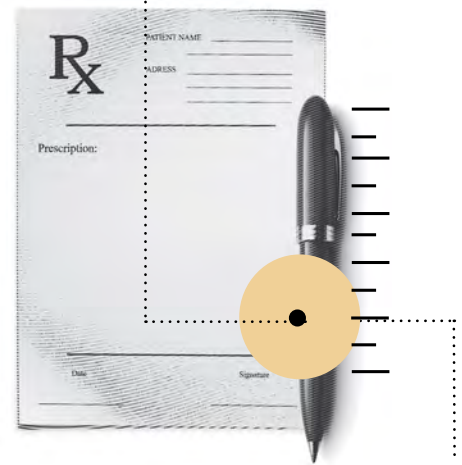
- ✓ Nonopioid therapy is preferred for chronic pain outside of active cancer, palliative, and end-of-life care.
- ✓ When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of opioid use disorder and overdose.
- ✓ Clinicians should always exercise caution when prescribing opioids and monitor all patients closely.

To develop the Guideline, CDC followed a transparent and rigorous scientific process using the best available scientific evidence, consulting with experts, and listening to comments from the public and partners.

As many as
1 in 4



patients receiving long-term **opioid therapy** in primary care settings



struggle with **opioid use disorder**.

PATIENT CARE AND SAFETY IS CENTRAL TO THE GUIDELINE

Before starting opioids to treat chronic pain, patients should:

- Make the most informed decision with their doctors
- Learn about prescription opioids and know the risks
- Consider ways to manage pain that do not include opioids, such as:
 - Physical therapy
 - Exercise
 - Nonopioid medications, such as acetaminophen or ibuprofen
 - Cognitive behavioral therapy (CBT)

CDC RECOMMENDATIONS

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

1

OPIOIDS ARE NOT FIRST-LINE THERAPY

Nonpharmacologic therapy and **nonopioid pharmacologic therapy** are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

2

ESTABLISH GOALS FOR PAIN AND FUNCTION

Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3

DISCUSS RISKS AND BENEFITS

Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Nonpharmacologic therapies and nonopioid medications include:

- Nonopioid medications such as acetaminophen, ibuprofen, or certain medications that are also used for depression or seizures
- Physical treatments (eg, exercise therapy, weight loss)
- Behavioral treatment (eg, CBT)
- Interventional treatments (eg, injections)

OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION

4

USE IMMEDIATE-RELEASE OPIOIDS WHEN STARTING

When starting opioid therapy for chronic pain, clinicians should prescribe **immediate-release opioids** instead of extended-release/long-acting (ER/LA) opioids.

5

USE THE LOWEST EFFECTIVE DOSE

When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 **morphine milligram equivalents (MME)/day**, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day.

6

PRESCRIBE SHORT DURATIONS FOR ACUTE PAIN

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

Immediate-release opioids: faster acting medication with a shorter duration of pain-relieving action

Extended release opioids: slower acting medication with a longer duration of pain-relieving action

Morphine milligram equivalents (MME)/day: the amount of morphine an opioid dose is equal to when prescribed, often used as a gauge of the abuse and overdose potential of the amount of opioid that is being given at a particular time

- 7 EVALUATE BENEFITS AND HARMS FREQUENTLY**
Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

ASSESSING RISK AND ADDRESSING HARMS

- 8 USE STRATEGIES TO MITIGATE RISK**
Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering **naloxone** when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent **benzodiazepine** use, are present.

Naloxone: a drug that can reverse the effects of opioid overdose

Benzodiazepine: sometimes called “benzo,” is a sedative often used to treat anxiety, insomnia, and other conditions

- 9 REVIEW PDMP DATA**
Clinicians should review the patient’s history of controlled substance prescriptions using state **prescription drug monitoring program (PDMP)** data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.

PDMP: a prescription drug monitoring program is a statewide electronic database that tracks all controlled substance prescriptions

- 10 USE URINE DRUG TESTING**
When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

- 11 AVOID CONCURRENT OPIOID AND BENZODIAZEPINE PRESCRIBING**
Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

- 12 OFFER TREATMENT FOR OPIOID USE DISORDER**
Clinicians should offer or arrange evidence-based treatment (usually **medication-assisted treatment** with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

NEARLY 2M
Americans, aged 12 or older, either abused or were dependent on prescription opioids in 2014

Medication-assisted treatment: treatment for opioid use disorder including medications such as buprenorphine or methadone